REMARKS

The Office Action requires restriction under 37 CFR §1.499 from among the following:

Group I:	claims 1-17, 21 and 33 (product by process), drawn to a binding moiety;
Group II:	Claims 18-19, drawn to a binding moiety linked to a diagnostic reagent;
Group III:	Claims 20-21, drawn to a multivalent reagent comprising two or more moieties;
Group IV:	Claims 22-25, drawn to a polynucleotide encoding a binding moiety, a vector comprising the polynucleotide, and a host cell;
Group V:	Claims 26-27, drawn to a method of producing a binding moiety;
Group VI:	Claim 28, drawn to a pharmaceutical composition;
Group VII:	Claim 29, drawn to a method of treating a pathological condition in a subject;
Group VIII:	Claim 30-32, drawn to a method of selecting a binding moiety.

Additionally, Applicants were required to elect a single species of non-antibody ligand, and a single type of antibody for examination.

Applicants elect, with traverse, the claims of Group I, CTLA-4 as a specific type of non-antibody ligand, and human antibodies as a specific type of antibody.

The Office Action alleges that the claims of the present invention are not linked so as to form a single inventive concept under PCT Rule 13.1. Allegedly, the claims of the present invention lack the same or corresponding special technical features as required under PCT Rule 13.2 because the special technical feature of the Group I claims is allegedly present in the prior art.

The special technical feature of the Group I claims is a binding moiety comprising a monomeric V-like domain in that at least one CDR loop is modified or replaced such that the solubility of the modified VLD is improved. The Office Action states that Pluckthun et al. "teach improving in vivo folding and stability of a single Fv antibody fragment by loop grafting." Office Action at 3.

Contrary to the assertions of the Office Action, the present invention is not described by Pluckthun et al. Specifically, Pluckthun et al., as stated above, relates to the grafting of CDR loop structures onto the framework of a humanized *antibody* scFv. The present invention relates to the modification of CDR loop structures on *non-antibody* domains. This difference alone proves that the present invention is not taught by Pluckthun.

The Office Action also states that "the CDRs from a fluorescein binding antibody were transplanted to the framework of humanized antibody" such that the "resulting antibody showed both (sic) a dramatic improvement in soluble expression." Office Action at 3-4. However, the improvements in soluble expression were not caused by the transplantation of the CDRs. Instead, the improvements in soluble expression were a direct result of the use of CDR loops from a different framework (4D5 scFv) than that of the fluorescein-binding antibody 4-4-20 to which they were transplanted. Pluckthun repeatedly refers to 4D5 scFv as being a "superior" framework, and it is this transplantation of CDR loops from a superior framework to the fluorescein-binding antibody that causes the increase in soluble expression.

In fact, the transplantation of the superior 4D5 scFv CDR loops to the fluorescein-binding antibody 4-4-20 results in decreased expression levels when compared to those associated with the original 4D5 scFv. As stated in Pluckthun, "...the CDRs do contribute as expected, to the physicochemical behaviour ...and in the present study the complete *in* vivo solubility of the original humanized 4D5 scFv ...was not mirrored by the graft." Essentially, this finding teaches away from transplanting CDR loops, and does not in any form teach or suggest the present invention wherein the physicochemical properties of a framework are improved by modification of the CDR loops **within** that framework. In the instant case, the solubility of a V-like binding domain is improved.

In summary, Puckthun involves enhancement of the solubility of an antibody domain by using a domain from a different framework, whereas the present invention is directed towards improving the solubility of a specific framework domain by modifying the CDRs within that domain. Therefore, the present invention is not disclosed or suggested by Puckthun, such that the special technical feature linking the claims is not known in the prior art.

In view of the fact that the Examiner's lack of unity objection is based on erroneous reasoning, all of the Groups of claims (or at least Groups I, III, IV, V, VI, VII and VIII) should

be rejoined in the present application. Consequently, reconsideration and withdrawal of the restriction requirement is respectfully requested.

Turning now to the election of species, the Office Action also requires election of a single species of non-antibody ligand and a single type of antibody. Allegedly, the species lack unity of invention because they are not so linked as to form a singly general inventive concept under PCT Rule 13.1.

To the contrary, the non-antibody ligands in question may be considered to be the single general inventive concept of T-cell surface proteins, while the antibodies in question also form a single inventive concept. Consequently, it is respectfully requested that the requirement for election of species be reconsidered and withdrawn.

In addition, enforcing the present restriction requirement would result in inefficiencies and unnecessary expenditures by both the Applicants and the PTO, as well as extreme prejudice to Applicants (particularly in view of GATT, a shortened patent term may result in any divisional or continuing applications filed). Restriction has not been shown to be proper, especially since the requisite showings have not been made in the Office Action and there are relationships between all of the pending claims. Indeed, the search and examination of each Group is likely to be co-extensive and, in any event, would involve such interrelated art such that the search and examination of the entire application can and should be made without. All of the foregoing, therefore, mitigate against restriction.

CONCLUSION

Reconsideration and withdrawal of the restriction requirement and election of species, and a favorable examination on the merits is respectfully requested in view of the remarks herein.

Respectfully submitted,

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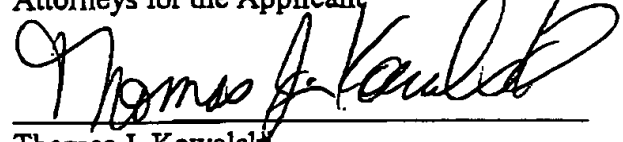
By: 

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